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The mode of action of tetraethylpyrophosphate at the cat's neuromuscular junction. By W. W. Douglas and W. D. M. Paton.
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Tetraethylpyrophosphate (TEPP) is known to cause neuromuscular block which is generally attributed to its cholinesterase-inhibiting properties but which has also been ascribed to a direct action by the drug at the neuromuscular junction.

Using the technique described by Burns & Paton (1951), we found that intravenous injections of TEPP (500 μg./kg.) were often followed by fluctuating depolarizations of the end-plate regions of the cat's gracilis. When depolarization did not occur spontaneously, it rapidly followed stimulation of the tied motor nerve to gracilis. In general, the degree of depolarization depended on the activity of the motor nerve, excited either by injury or electrically. With bigger doses of TEPP depolarization always occurred, and was large and persistent. The depolarizations observed were fully adequate to account for the neuromuscular block produced by TEPP. They were similar in magnitude to those produced by blocking doses of acetylcholine or decamethonium, but differed in the time of onset and the course of the depolarization. In addition, TEPP differs from these directly acting substances by its failure to elicit a twitch of the tibialis when injected close arterially, even in a dose which was followed by a complete and prolonged neuromuscular block. These results indicate that the depolarizing action of TEPP is indirect.

The only fact suggesting a direct action is that TEPP, in yet larger doses (10 mg./kg.) given intravenously, can still evoke a slowly developing depolarization of a muscle denervated 4–6 days previously to exclude liberation of acetylcholine at the nerve endings of the muscle. But this depolarization is, in fact, due to the accumulation of acetylcholine from other sites, particularly from the bowel. Blood from animals receiving these large doses of TEPP was found to contain as much as 40 mμg. acetylcholine/ml.

Neuromuscular block caused by TEPP is due, therefore, to acetylcholine produced either locally at motor nerve endings or at sites remote from the muscle. No direct action by TEPP was detected or need be postulated to account for its neuromuscular effects. These experiments emphasize, in addition, the care that must be taken in interpreting the local effects of anticholinesterases when these drugs are given systemically.

REFERENCE

Burns, B. D. & Paton, W. D. M. (1951). *J. Physiol.* **115**, 41.